THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Gregson J, Kaleebu P, Marconi VC, et al. Occult HIV-1 drug resistance to thymidine analogues following failure of first-line tenofovir combined with a cytosine analogue and nevirapine or efavirenz in sub Saharan Africa: a retrospective multi-centre cohort study. *Lancet Infect Dis* 2016; published online Nov 30. http://dx.doi.org/10.1016/S1473-3099(16)30469-8.

Supplementary Table 1: Characteristics of studies from the TenoRes collaboration included in the present analysis

Study	Country	Income region	Study type	Underlying cohort exclusively first line treated?	Follow-up Active* or passive	N	TDF resistance	VL threshold for genotype	Use of FTC	Use of NVP	Baseline CD4 <100	Baseline viral load >100,000
Sub Saharan Africa												
ACTION	Nigeria	LMIC	Cohort	Yes	Passive	17	10	1000	17 (100%)	7 (41%)	10 (59%)	-
ACTION Plus UP,	Nigeria	LMIC	Cohort	Yes	Passive	21	17	1000	18 (86%)	12 (57%)	8 (38%)	-
Doris Duke Study	Nigeria	LMIC	Trial	Yes	Active	13	8	1000	0 (0%)	3 (23%)	5 (38%)	7 (54%)
Harvard/APIN PEPFAR	Nigeria	LMIC	Cohort	No	Active	20	15	2000	18 (90%)	19 (95%)	16 (80%)	17 (85%)
CDC Nigeria ADR	Nigeria	LMIC	Cohort	Yes	Passive	6	3	1000	5 (83%)	6 (100%)	2 (33%)	4 (67%)
Lubumbashi,	DRC	LIC	Trial	Yes	Active	12	6	1000	12 (100%)	12 (100%)	7 (58%)	9 (75%)
UVRI/MoH Uganda surveillance study	Uganda	LIC	Cohort	Yes	Passive	35	19	1000	18 (51%)	24 (69%)	18 (51%)	29 (83%)
CDC Uganda ADR	Uganda	LIC	Cohort	Yes	Passive	5	3	1000	4 (80%)	3 (60%)	2 (40%)	-
CDC/MoH, Tanzania	Tanzania	LIC	Cohort	No	Active	15	3	1000	12 (80%)	1 (7%)	-	-
CDC Kenya ADR	Kenya	LMIC	Cohort	Yes	Passive	43	31	1000	1 (2%)	27 (63%)	17 (40%)	-
TDF AMPATH	Kenya	LMIC	Cohort	Yes	Active	27	19	1000	0 (0%)	23 (85%)	-	-
PASER	Nigeria, Uganda, South Africa, Kenya, Zambia, Zimbabwe	LMIC	Cohort	No	Active	53	19	1000	52 (98%)	17 (32%)	27 (51%)	35 (66%)
Aurum, KZN	South Africa	HMIC	Cohort	No	Active	11	0	1000	9 (82%)	3 (27%)	1 (9%)	0 (0%)
Africa Centre, KZN	South Africa	HMIC	Cohort	No	Passive	64	45	1000	0 (0%)	10 (16%)	32 (50%)	-
Bloemfontein,	South Africa	HMIC	Cohort	No	Passive	78	59	1000	2 (3%)	16 (21%)	14 (18%)	1 (1%)
RFVF, Durban	South Africa	HMIC	Cohort	Yes	Passive	51	34	1000	0 (0%)	7 (14%)	26 (51%)	0 (0%)
CDC/NCID, KZN,	South Africa	HMIC	Cohort	Yes		98	49	1000	0 (0%)	33 (34%)	-	-
MSF	Swaziland	HMIC	Cohort	No	Active	22	12	1000	0 (0%)	5 (23%)	10 (45%)	6 (27%)
CDC Zambia ADR	Zambia	LMIC	Cohort	No	Passive	14	8	1000	13 (93%)	1 (7%)	4 (29%)	-
OCTANE	Kenya, Botswana, Malawi, South Africa, Zambia, Zimbabwe	LMIC	Trial	Yes	Active	36	7	2000	36 (100%)	36 (100%)	16 (44%)	27 (75%)

Supplementary Table 2: Number of patients with available data for covariates and number of patients contributing to subgroup analyses.

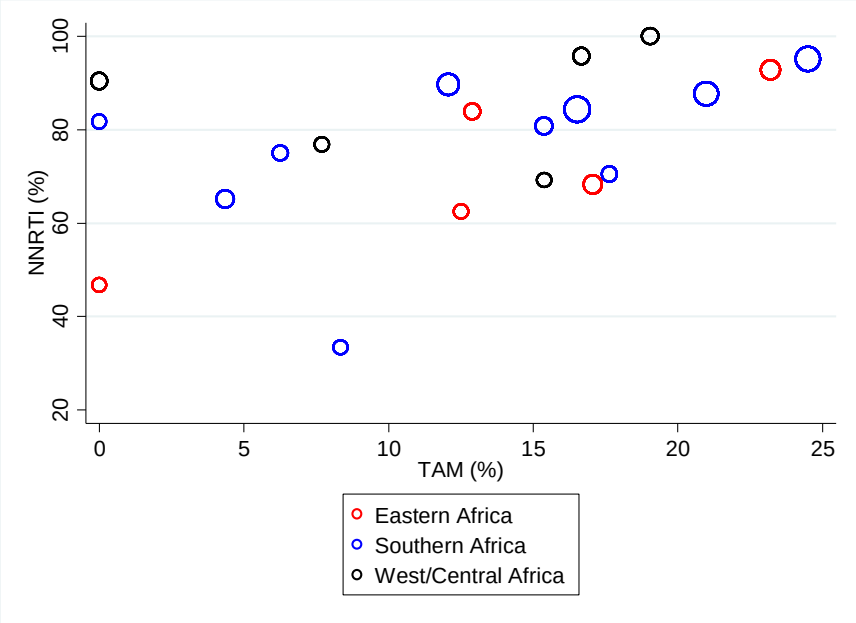
Study	N	N with information on CD4 or viral load		Patients contributing to subgroup analyses											
				NRTI		Gender		NNRTI		Baseline CD4 (cells/mm3)			Viral load (log10 HIV1-RNA/ml)		
		Base-line CD4	Base-line viral load	3TC	FTC	Female	Male	EFV	NVP	Unavail-able	<100	>100	Unavai-lable	<5	>5
Eastern Africa	**159**	**108**	**57**	**38**	**104**	**76**	**62**	**98**	**42**	**36**	**55**	**53**	**87**	**8**	**48**
CDC Kenya ADR	56	51	0	0	55	36	20	36	20	5	24	27	56	0	0
CDC/MoH, Tanzania	15	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PASER Uganda	16	16	16	15	0	0	10	6	10	0	9	7	0	0	15
TDF AMPATH, Kenya	31	0	0	0	31	18	13	27	0	31	0	0	31	0	0
UVRI/MoH Uganda surveillance study	41	41	41	23	18	22	19	29	12	0	22	19	0	8	33
Southern Africa	**461**	**248**	**101**	**58**	**379**	**266**	**146**	**82**	**333**	**198**	**109**	**96**	**356**	**38**	**22**
Africa Centre, South Africa	81	71	0	0	81	62	19	0	70	0	42	29	81	0	0
Aurum, South Africa	12	11	11	0	0	0	0	0	0	0	0	0	0	0	0
Bloemfontein, South Africa	102	26	5	3	99	62	40	19	83	76	18	8	97	0	0
CDC Zambia ADR	17	14	0	16	0	11	6	3	14	0	0	10	17	0	0
Durban, South Africa	58	51	12	0	58	25	33	0	51	7	29	22	46	12	0
KZN, South Africa	115	0	0	0	115	64	38	38	77	115	0	0	115	0	0
MSF Swaziland	26	26	25	0	26	16	10	6	20	0	13	13	0	17	8
OCTANE South Africa	16	16	16	16	0	16	0	16	0	0	7	0	0	0	14
PASER South Africa	11	10	11	0	0	0	0	0	0	0	0	0	0	0	0
PASER Zambia	23	23	21	23	0	10	0	0	18	0	0	14	0	9	0
West/Central Africa	**92**	**89**	**50**	**56**	**13**	**27**	**33**	**50**	**20**	**0**	**37**	**20**	**21**	**12**	**29**
ACTION Plus UP, Nigeria	21	20	0	0	0	0	0	0	0	0	0	0	0	0	0
ACTION, Nigeria	21	19	0	21	0	0	15	10	11	0	14	0	21	0	0
Lubumbashi, DRC	13	13	13	13	0	8	0	13		0	0	6	0	0	10
Doris Duke study, Nigeria, Kanki	13	13	13	0	13	7	6	4	9	0	5	8	0	7	0
	24	24	24	22	0	12	12	23	0	0	18	6	0	5	19

Supplementary Table 3: Information on drug resistance and baseline characteristics of participants by HIV-1 subtype. Note that subtype AG is also known as CRF_02

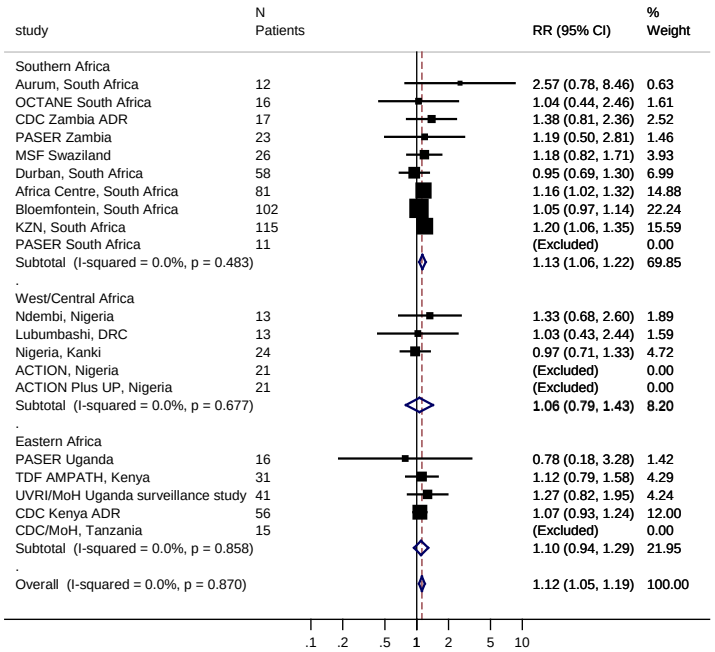
Subtype	N	TAM, N (%)	TDF resistance, N (%)	EFV or NVP resistance, N(%)	Lamivudine resistance, N(%)	NVP use, N(%)	FTC use, N(%)	Baseline CD4 (cells/mm3), median (IQR)	Baseline viral load (log10/ml), median (IQR)
A	90	21 (23.3%)	52 (57.8%)	73 (81.1%)	60 (66.7%)	65 (72.2%)	25 (27.8%)	113.0 (50.0 to 223.0)	5.6 (5.2 to 5.9)
AG/G	49	10 (20.4%)	38 (77.6%)	46 (93.9%)	44 (89.8%)	33 (67.3%)	37 (75.5%)	66.0 (30.0 to 126.0)	5.2 (4.7 to 5.5)
C	481	80 (16.6%)	293 (60.9%)	404 (84.0%)	305 (63.4%)	122 (25.4%)	87 (18.1%)	93.5 (34.0 to 159.0)	4.8 (3.6 to 5.5)
D	42	3 (7.1%)	30 (71.4%)	30 (71.4%)	31 (73.8%)	22 (52.4%)	23 (54.8%)	77.0 (25.5 to 178.5)	5.6 (5.0 to 5.8)
Other	50	1 (2.0%)	32 (64.0%)	42 (84.0%)	38 (76.0%)	28 (56.0%)	32 (64.0%)	92.0 (26.0 to 221.0)	5.4 (5.1 to 5.9)

Supplementary Figure 1: a) Scatter of study-level prevalence of NNRTI resistance and prevalence of TAM by region. Markers are weighted by study size. (Spearman's rho=0.62 p<0.0001); **b)** meta-analysis of odds ratios for NNRTI resistance in participants with TAM versus those without TAM within individual studies

a)

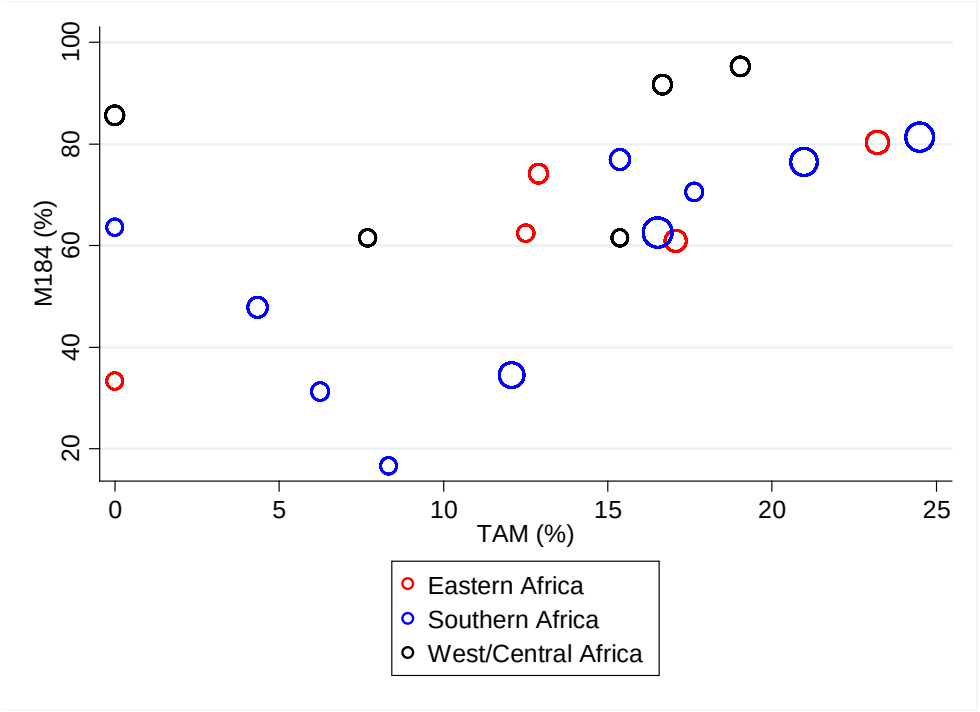


b)

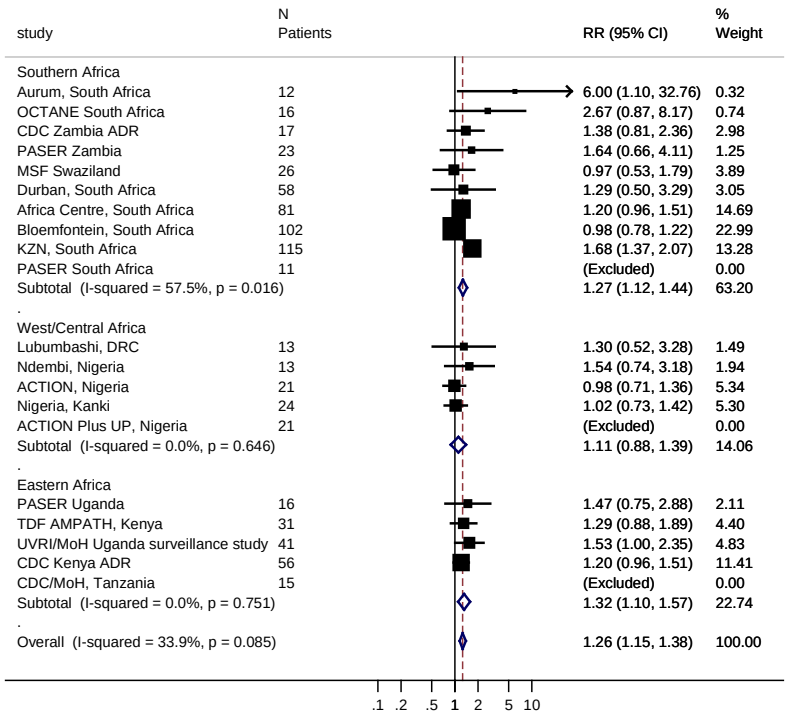


Supplementary Figure 2: a) Scatter of study-level prevalence of lamivudine resistance and prevalence of TAM by region. Markers are weighted by study size. (Spearman's rho=0.65 p<0.0001; **b)** meta-analysis of odds ratios for lamivudine resistance in participants with TAM versus those without TAM within individual studies

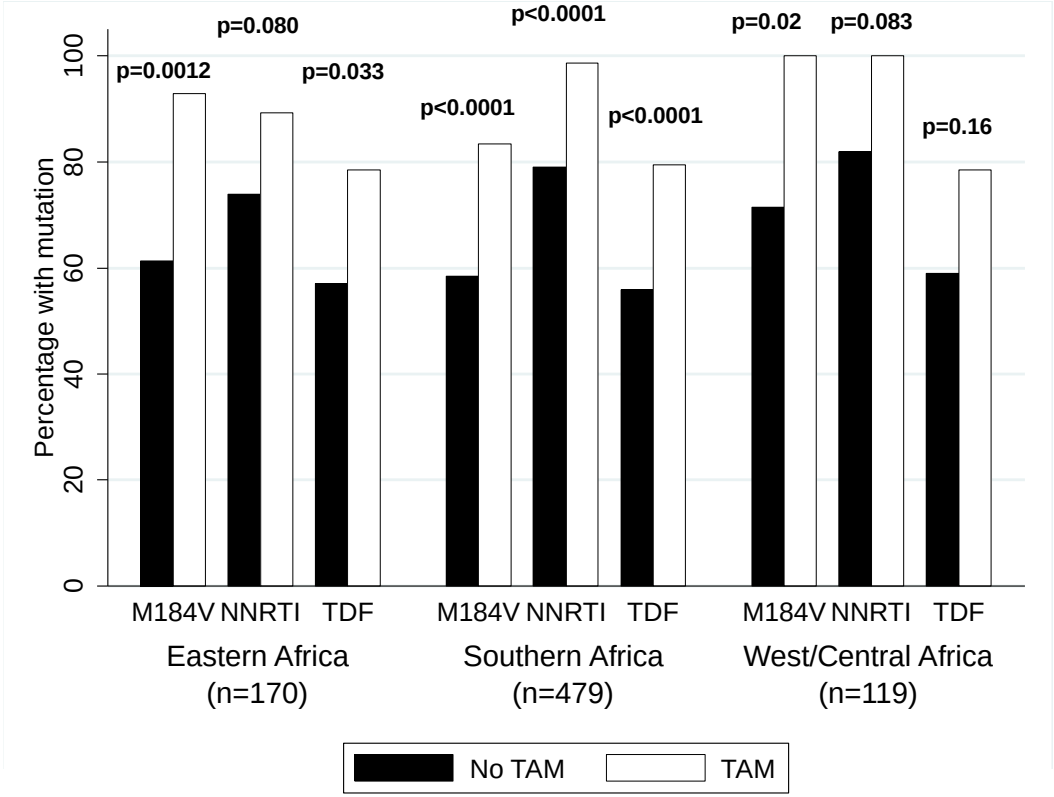
b)



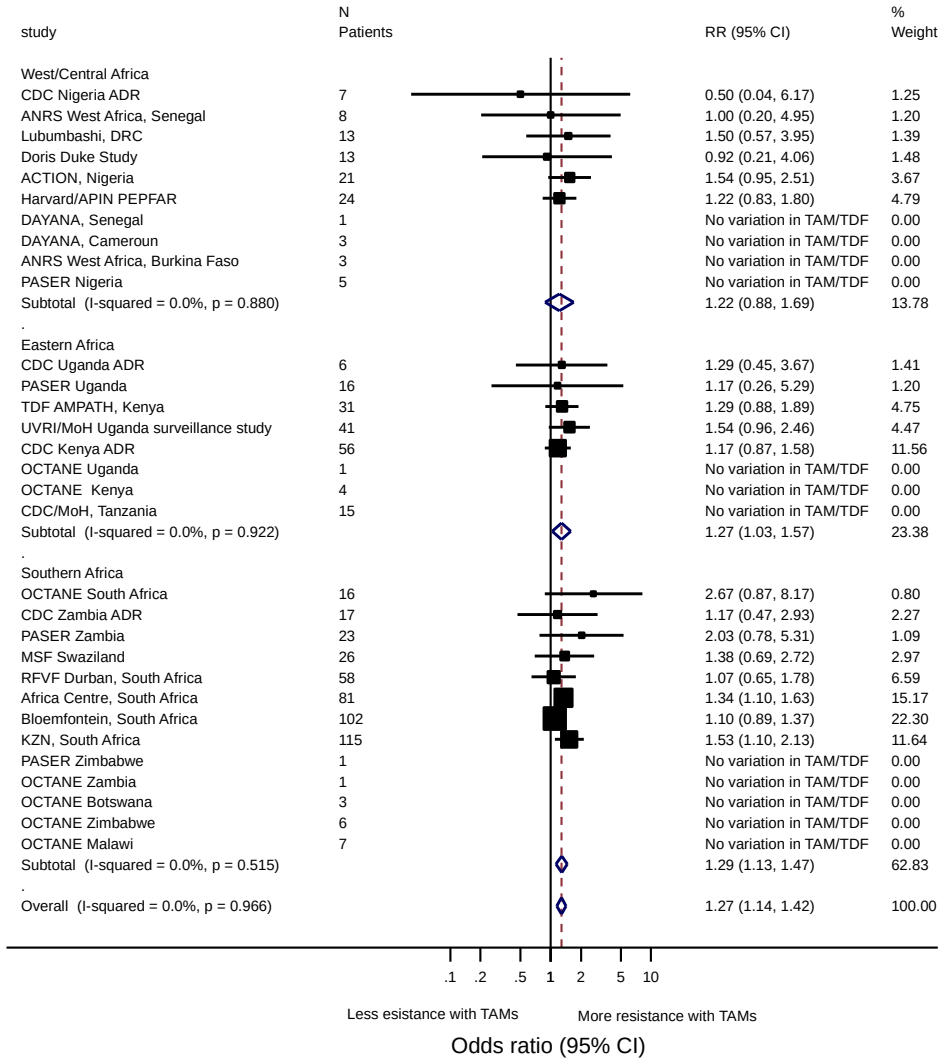
b)



Supplementary Figure 3: Estimated prevalence of drug resistant mutations, sensitivity analyses including all participants from studies in sub-Saharan Africa (including those with <10 patients)



Supplementary Figure 4: Within study comparison of tenofovir resistance by presence or absence of TAMs; sensitivity analyses including all participants from studies in sub-Saharan Africa (including those with <10 patients)



Study Groups

Uganda Virus Research Institute/Ministry of Health (UVRI/MoH) Uganda surveillance study: Fred Lyagoba, Tom Lutalo', Anne, Kapaata, Faith Nanyonga, Chris Parry, Norah Namuwenge, Robert Downing, The HIV Drug Resistance Working group and participants and study teams from the treatment centers at Masaka and Mbale regional referral hospitals and Nsambya Home-Care.

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